Marked-Up Copy of Amended Claim

4. (Amended) An isolated nucleic acid molecule consisting of a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence that encodes a protein comprising the amino acid sequence of SEQ ID NO:2;

(b) a nucleotide sequence [nucleic acid molecule] consisting of the nucleic acid sequence of SEQ ID NO:1; and

(c) a nucleotide sequence [nucleic acid molecule] consisting of the nucleic acid sequence of SEQ ID NO:3[; and

(d) a nucleotide sequence that is completely complementary to a nucleotide sequence of (a)-(c)].

REMARKS

Rejection under 35 USC § 112, second paragraph:

The Examiner rejected Claim 24 because the specification does not teach how to recombinantly produce a polypeptide from the complementary nucleic acid. Applicants hereby amended claim 4 by deleting subsection (d), and added a dependent claim 30 drawn to a complementary nucleic acid molecule.

Rejection under 35 USC §101 and §112, 1st paragraph:

The Examiner has rejected claims 4, 8, 9, and 24-29 under 35 U.S.C.§101 and §112, 1st paragraph. In summary, the Examiner has stated that the claimed isolated nucleic acid molecules lack a credible, specific and substantial utility or a well-established utility and, consequently, one skilled in the art would not know how to use the claimed invention.

On page 4 of the Office Action, the Examiner states that no well-established utility exists for newly isolated complex biological molecules. The Examiner states that the specification does not disclose experiments that impart any function for the putative receptor polypeptide encoded by the claimed nucleotide in the context of the cell or organism. The specification does not teach the skilled artisan how to use the receptor peptide for any unique or specific purpose, such as second-messenger assays.

Further, the Examiner stated that the polypeptide of the instant specification and the polynucleotide encoding [SEQ ID NO: 2] are unidentified molecules. It possesses only low/moderate homology to known GPCR protein (page 4, second paragraph).

Moreover, the Examiner stated that there is no evidence that the protein disclosed in the instant specification functions as a GPCR protein and additional specific functional assays would be needed since this family of proteins is very large and enormously varied.

Finally, the Examiner stated that one skilled in the art would not know the utility and function of the polypeptide disclosed in the instant disclosure, because a GPCR could mediate hundreds or thousands of physiological functions involving cell- to-cell communication as the initial event.

Applicants respectfully disagree with the rejections.

Applicants would like to direct Examiner's attention to recently discovered articles authored by Bunzow et al (Mol Pharmacol 2001 Dec;60(6):1181-8) and Borowsky et al. (PNAS, 2002 June; 98, 8966-8971).

In a sequence homology search, Applicants found SEQ ID NO: 2 of the instant invention shares a 99% sequence homology with the protein sequences studied in both references. Exhibition A discloses a sequence alignment of SEQ ID NO: 2 and the sequence of human trace amine receptor studied by Bunzow et al (called hTAR) (see attached Exhibition A) or Borowsky et al (called human TA1). The sequence alignment shows that position 1 through position 338 of SEQ ID NO: 2 is 100% aligned to position 2 through position 339 of hTAR/human TA1. Through the sequence comparison, both references revealed that Met at position 1 of hTAR/human TA1 is not within a conserved functional domain of this receptor.

Human trace amine receptor disclosed in both references belongs to aminergic GPCR subfamily. (see Kim and Zastrow, Molecular Pharmacology, 60(6), 1165-1167, 2001). Through the sequence comparison, this protein shares most of the functional domains with GPCR 58 (see Bunzow et al, Figure 1, Borowsky et al, Figure 1).

Borowsky et al disclose that human TA1 is potently activated by tyramine and beta – phenylethylamine (PEA) and is a true neurotransmitter that associated with depression as well as other psychiatric disorders (see abstract, introduction). In addition, human TA1 mRNA is expressed in low to moderate levels in peripheral tissues such as stomach, kidney, and lung, and within the CNS appears to be restricted primarily to the amygdala (see page 8970, column 2, last paragraph).

Bunzow et al did pharmacological characterization of the rat trace amine receptor and found that a rat TAR stimulates cAMP production when exposed to the trace amines such as p-tyramine and beta-PEA. Moreover, Figure 1 shows that rat TAR and human TAR shares substantially same GPCR functional domains.

As stated in the specification, the present invention is related to the aminergic (biogenic amines) receptor subfamily of the GPCR family (see page 2, first paragraph). The utility of the receptor of the present invention is depicted on pages 4-9, specifically it is associated with psychiatric diseases (see page page 4, second paragraph, and page 5, second paragraph). Thus, this receptor would be a potential drug target for neurotransmitter related diseases.

Support for the functional classification of the protein of SEQ ID NO:2 as being a member of aminergic receptor of GPCR can also be found in Figure 2. For example, the Blast alignment shows that SEQ ID NO:2 shares most of the functional domains with GPCR 58. In addition, Hmmer search results (pfam.wustl.edu) on page 2 of Figure 2 shows that SEQ ID NO: 2 of the present invention has statistically significant homology to serotonin receptors and dopamine receptors in the aminergic receptor domains.

Moreover, the receptor of the present invention has substantial the same expression profile as disclosed in the reference by Borowsky et al., for example, the expression in stomach, kidney, as well as in brain.

In summary, supported by references disclosed above, the present invention meets the requirement of a specific, substantial and credible utility that is imposed by the Utility Guideline under 35 USC §101 and §112, 1st paragraph.

Conclusion

Applicants would like to thank Examiner Wegert and Examiner Kemmerer for the courteous interview with their representative Lin Sun-Hoffman on September 24, 2002. As suggested by both examiners, Applicants hereby submit the article authored by Borowsky et al and Bunzow et al, as well as a review article authored by Kim and Zastrow for Examiners' review. All these references provide supporting utility evidence to the claims of the present invention.

In view of the above remarks and amendments, Applicants respectfully submit that the application and claims are in condition for allowance, and request that the Examiner reconsider and withdraw the rejections. If for any reason the Examiner finds the application in condition for allowance, the Examiner is invited to call the undersigned to expedite prosecution of the application.

Respectfully submitted,

Date: Oct. 9, 2002

By: _____
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Attachment: Exhibition A

Exhibition A: Alignment of SEQ ID NO: 2 and hTAR of Bunzow et al (2001)

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>CRA|334000045891168 /altid=gi|21264324 /def=ref|NP_612200.1|
          (NM_138327) trace amine receptor 1 [Homo sapiens]
          /org=Homo sapiens /taxon=9606 /div=PRI /dataset=nraa
          /length=339
         Length = 339

 Score =  705 bits (1801), Expect = 0.0
 Identities = 338/338 (100%), Positives = 338/338 (100%)

Query: 1   MPFCHNIINISCVKNNWSNDVRASLYSLMVLIILTTLVGNLIVIVSISHFKQLHTPTNWL 60
           MPFCHNIINISCVKNNWSNDVRASLYSLMVLIILTTLVGNLIVIVSISHFKQLHTPTNWL
Sbjct: 2   MPFCHNIINISCVKNNWSNDVRASLYSLMVLIILTTLVGNLIVIVSISHFKQLHTPTNWL 61

Query: 61  IHSMATVDFLLGCLVMPYSMVRSAEHCWYFGEVFCKIHTSTDIMLSSASIFHLSFISIDR 120
           IHSMATVDFLLGCLVMPYSMVRSAEHCWYFGEVFCKIHTSTDIMLSSASIFHLSFISIDR
Sbjct: 62  IHSMATVDFLLGCLVMPYSMVRSAEHCWYFGEVFCKIHTSTDIMLSSASIFHLSFISIDR 121

Query: 121 YYAVCDPLRYKAKMNILVICVMIFISWSVPAVFAFGMIFLELNFKGAEEIYYKHVHCRGG 180
           YYAVCDPLRYKAKMNILVICVMIFISWSVPAVFAFGMIFLELNFKGAEEIYYKHVHCRGG
Sbjct: 122 YYAVCDPLRYKAKMNILVICVMIFISWSVPAVFAFGMIFLELNFKGAEEIYYKHVHCRGG 181

Query: 181 CSVFFSKISGVLTFMTSFYIPGSIMLCVYYRIYLIAKEQARLISDANQKLQIGLEMKNGI 240
           CSVFFSKISGVLTFMTSFYIPGSIMLCVYYRIYLIAKEQARLISDANQKLQIGLEMKNGI
Sbjct: 182 CSVFFSKISGVLTFMTSFYIPGSIMLCVYYRIYLIAKEQARLISDANQKLQIGLEMKNGI 241

Query: 241 SQSKERKAVKTLGIVMGVFLICWCPFFICTVMDPFLHYIIPPTLNDVLIWFGYLNSTFNP 300
           SQSKERKAVKTLGIVMGVFLICWCPFFICTVMDPFLHYIIPPTLNDVLIWFGYLNSTFNP
Sbjct: 242 SQSKERKAVKTLGIVMGVFLICWCPFFICTVMDPFLHYIIPPTLNDVLIWFGYLNSTFNP 301

Query: 301 MVYAFFYPWFRKALKMMLFGKIFQKDSSRCKLFLELSS 338
           MVYAFFYPWFRKALKMMLFGKIFQKDSSRCKLFLELSS
Sbjct: 302 MVYAFFYPWFRKALKMMLFGKIFQKDSSRCKLFLELSS 339
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